REMARKS

Claims 18-25, 28 and 39-58 were pending in this application. Claim 18 has been amended. Claims 19 and 20 have been canceled without prejudice herein. Claims 39-58 have been withdrawn as being drawn to a non-elected invention. Support for amended claim 18 can be found at least, for example, at paragraph [054] and [140]. Accordingly, upon entry of this amendment, claims 18-25, 28 and 39-58 will pending in this application.

Cancellation of and/or amendments to the claims should in no way be construed as acquiescence to any of the Examiner's rejections and were done solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in another patent application(s).

Election/Restriction

It is Applicants understanding that upon the indication of allowable subject matter, Applicants will be entitled to rejoinder of claims 39-58, which ultimately depend from claim 18.

Rejection of claims 18, 21-25 and 28 Under 35 U.S.C. §112, first paragraph

Claims 18, 21-25 and 28 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement because, according to the Examiner, "while being enabling for various compositions that comprise polyclonal antibodies and monoclonal antibodies to ribitol teichoic acid of S. aureus, does not reasonably provide enablement for the specific combinations of monoclonal antibodies which have non-identical amino acid sequences, as well as chimeric, humanize [sic] antibodies and ribitol teichoic acid antigen binding fragments thereof."

This rejection is respectfully traversed, however, in the interest of expediting prosecution, the claims have been amended.

Specifically, claim 18 has been amended to recite a pharmaceutical composition comprising a therapeutically effective amount of a monoclonal antibody or an antigen binding fragment thereof that specifically binds to ribitol phosphate wall teichoic acid (WTA) of *S. aureus,* wherein said therapeutically effective amount of said antibody or

fragment thereof alleviates or blocks colonization or infection by *S. a ureus* upon administration to a patient.

The Examiner recognizes that the specification is "enabling for various compositions that comprise polyclonal antibodies and monoclonal antibodies to ribitol teichoic acid of *S. aureus*." Applicants assert that the specification is also enabling for chimeric, humanized and ribitol teichoic acid antigen-binding fragments thereof. Specifically, Applicants teach at least at paragraphs [064]-[066] and [0136] how to make chimeric antibodies. Applicants teach at least at paragraph [070] and [0137] how to make humanized antibodies. Applicants teach at least at paragraph [040] how to make antigen binding fragments, *e.g.,* Fab, Fab', F(ab')2, Fv, SFv, and scFv. Further, at the time of filing, it was well-known to one skilled in the art how to generate chimeric antibodies, humanized antibodies and antigen binding fragments. For example, several different methodologies were known in the art for making humanized antibodies prior to the filing date of the instant application, see, *e.g.,* Queen *et al.*, *Proc. Natl. Acad. Sci. USA* 86:10029-10033 (1989), US 5,530,101, US 5,585,089, US 5,693,761, US 5,693,762, Selick *et al.*, WO 90/07861, and Winter, US 5,225,539. Moreover, methods of making antigen-binding fragments of antibodies were within the skill of the art, see, *e.g.,* Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269 315 (1994), Ward *et al.* (1989) *Nature* 341:544-546; Bird *et al.* (1988) *Science* 242:423-426; and Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883.

In order to satisfy the enablement requirement, the specification need not disclose what is well-known to those skilled in the art. *Chiron Corp. v. Genentech, Inc.,* 363 F.3d 1247, 1254 (Fed. Cir. 2004), *cert. denied,* 543 U.S. 1050 (2005). The court in Chiron held that because chimeric antibodies were considered nascent technology at the time of filing of the patent at issue, undue experimentation would be required to make and use the claimed chimeric antibodies. *Id.* at 1256-57. Unlike Chiron, and as noted above, methods of making and using chimeric antibodies, humanized antibodies and antigen-binding fragments were well-known in the art at the time of filing the instant specification. Therefore, the disclosure of the instant specification is commensurate in scope with the claims.

Based on the teachings in the specification and the state of the art at the time of filing, one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation. Accordingly, Applicants respectfully request that the rejection of the claims under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection of claims 18-19 and 28 Under 35 U.S.C. §102(b) – Vorland et al.

Claims 18-19 and 28 have been rejected under 35 U.S.C. §102(b) as being anticipated by Vorland *et al.* (1998).

In order to anticipate a claim under §102(b), a single prior art reference must disclose, either expressly or inherently, each and every limitation of the claim. *Atlas Powder Co. v. IRECO, Inc.,* 190 F.3d 1342, 1346 (Fed. Cir.1999). Under principles of inherency, "if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Mehl/Biophile Int'l Corp. v. Milagraum,*192 F.3d 1362, 1365 (Fed Cir. 1999). The fact that a certain result or characteristic *may* occur in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir.1993). Instead, the reference includes an inherent characteristic if it is "the natural result flowing from the reference's explicitly explicated limitations." *Eli Lilly & Co. v. Barr Lab.,* 251 F.3d 955, 970 (Fed. Cir. 2001).

As set forth above, the claims presently under examination are directed to pharmaceutical compositions comprising a therapeutically effective amount of a monoclonal antibody or an antigen binding fragment thereof that specifically binds to ribitol phosphate wall teichoic acid (WTA) of *S. aureus,* wherein said therapeutically effective amount of said antibody or fragment thereof alleviates or blocks colonization or infection by *S. aureus* upon administration to a patient.

The Vorland *et al.* reference cited by the Examiner under 102(b) discloses blocking experiments in which anti-teichoic acid antibodies blocked the activity of lactoferricin B (Lf-cin B), which is an antimicrobial peptide. The antibody used in the Vorland experiments was anti-staphylococcal ribitol TA from Meridian Diagnostics, Inc. of Cincinnati, OH. (See *Reagents* section of *Materials and Methods* on page 468, column 1). That antibody is a polyclonal antibody supplied as human serum not a monoclonal antibody as required by the amended claims (see the product sheet attached as Appendix A). In addition, the antibody used by Vorland et al.

contains sodium azide, a toxic agent, as a preservative and, therefore, is not a pharmaceutical composition.

In summary, Applicants respectfully submit that the claimed invention is not anticipated by the teachings of Vorland *et al.* on the grounds that the reference does not suggest each and every element of the claimed invention. Thus, Applicants respectfully request that the rejection of claims 18-19 and 28 be reconsidered and withdrawn.

Rejection of claims 18-19 Under 35 U.S.C. §102(b) – White et al.

Claims 18-19 have been rejected under 35 U.S.C. §102(b) as being anticipated by White *et al.* (1983). The Examiner states that "[t]he anti-ribitol teichoic acid antibody compositions of White et al inherently anticipate the instantly claimed invention directed to compositions of antibodies specific for ribitol teichoic acid of Staphylococcus aureus." This rejection is respectfully traversed.

As stated above, the claims presently under examination are directed to a pharmaceutical composition comprising a therapeutically effective amount of a monoclonal antibody or an antigen binding fragment thereof that specifically binds to ribitol phosphate wall teichoic acid (WTA) of *S. aureus,* wherein said therapeutically effective amount of said antibody or fragment thereof alleviates or blocks colonization or infection by *S. aureus* upon administration to a patient.

In contrast, White *et al.* disclose the use of a purified antigen, *e.g.,* teichoic acid, in detecting antibodies to teichoic acid in human sera. White *et al.* disclose that detection of anti-teichoic acid antibodies in human sera by agar gel diffusion requires a purified antigen or antibody. In this test, White *et al.* used a known positive polyclonal antiserum as a positive control. Similar to Vorland *et al.,* White *et al.* also fail to teach or suggest monoclonal anti-teichoic antibodies as required by the pending claims.

In summary, Applicants respectfully submit that the claimed invention is not anticipated, expressly or inherently, by the teachings of White *et al.* on the grounds that the reference does not suggest each and every element of the claimed invention. Thus, Applicants respectfully request that the rejection of claims 18-19 be reconsidered and withdrawn.

Rejection of claims 18-19 Under 35 U.S.C. §102(b) – Godin et al.

Claims 18-19 have been rejected under 35 U.S.C. §102(b) as being anticipated by von Godin *et al.* (1980).

Von Godin *et al.* disclose polyclonal antisera to polysaccharide A, *i.e.*, ribitol teichoic acid that have been absorbed with pronase-treated staphylococcal reference strains. Treatment with pronase removed protein A from the absorbing staphylococci and prevented loss of specific antibodies. Von Godin *et al.* fail to teach or suggest monoclonal antibodies or antigen binding fragment thereof that specifically binds to wall teichoic acid (WTA) of *S. aureus.*

In summary, Applicants respectfully submit that the claimed invention is not anticipated by the teachings of von Godin *et al.* on the grounds that the reference does not suggest each and every element of the claimed invention. Thus, Applicants respectfully request that the rejection of claims 18-19 be reconsidered and withdrawn.

Rejection of claims 18-25 and 28 Under 35 U.S.C. §103(a)

Claims 18-25 and 28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Fischer et al. (US Pat. 6,939,543) in view of Patti (US Pat. 6,703,025). According to the Office Action, "it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the compositions of Fischer et al to include anti-ribitol teichoic acid antibodies in view of the guidance and teaching of Patti et al."

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.*** See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469 (Fed.Cir. 1988).

The subject matter of the pending claims is set forth above. As set forth in the previous response, the Fischer *et al.* patent cited by the Examiner under 103(a) teaches, *inter alia*,

antibodies that bind to glycerol phosphate lipoteichoic acids (LTA) of Staphylococci, including *S. aureus* and *S. epidermidis*. The reference fails to teach monoclonal antibodies that specifically binds to ribitol phosphate wall teichoic acid (WTA) of *S. aureus*.

The Patti *et al.* patent cited by the Examiner under 103(a) teaches multicomponent vaccines which aid in the treatment of staphylococcal infections and which include selected combinations of bacterial binding proteins, or antibodies to those proteins. Patti *et al.* teach a composition that includes bacterial binding proteins in combination with a bacterial component, *preferably* capsular polysaccharides type 5 or type 8, to increase the rate of opsonization and phagocytosis of *S. aureus* (see column 22, lines 30-35). Patti *et al.* further teach that some *S. aureus* strains have capsules which act to inhibit phagocytosis unless specific antibodies are present. Although Patti *et al.* teach that teichoic acids can be antigenic, Patti *et al.* fail to teach or suggest that anti-teichoic acid antibodies could be protective, *e.g.*, alleviate or block colonization by *S. aureus*. Patti *et al.* merely teach that anti-teichoic antibodies can be found in patients with active endocarditis due to *S. aureus* (see column 22, lines 48-52) and does not teach monoclonal antibodies that recognize ribitol phosphate wall teichoic acid (WTA) of *S. aureus* as required by the pending claims. In fact, the only reference to monoclonals antibodies relates ***specifically to antibodies specific for MSCRAMM peptides***, not to antibodies that bind to ribitol phosphate wall teichoic acid (WTA). The reference further fails to provide any suggestion that antibodies to teichoic acid provide for increase opsonization and phagocytosis.

As neither reference teaches monoclonal antibodies that bind to ribitol phosphate wall teichoic acid (WTA) of *S. aureus*, the references fail to teach or suggest all the claim limitations. In addition, given the teachings of Patti, there would have been no motivation to modify the teachings of Fischer to make the claimed pharmaceutical compositions comprising a therapeutically effective amount of a monoclonal antibody or an antigen binding fragment thereof that specifically binds to ribitol phosphate wall teichoic acid (WTA) of *S. aureus*, wherein said therapeutically effective amount of said antibody or fragment thereof alleviates or blocks colonization by *S. aureus* upon administration to a patient. Prior to the instant invention, there was no indication that WTA was specifically involved in *S. aureus* disease or colonization. Therefore, given the teachings of Fischer and Patti, there would have been no reasonable expectation of success in alleviating or blocking colonization or infection by *S. aureus* using such compositions. In summary, Applicants respectfully submit that the claimed invention is not

obvious in view of Fischer *et al.* and Patti *et al.* on the grounds that the references do not teach or suggest each and every element of the claimed invention. Thus, Applicants respectfully request that the rejection of claims 18-25 and 28 be reconsidered and withdrawn.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Dated: May 7, 2007

Respectfully submitted,

By _____

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Appendix A

Endo-Staph®

TEICHOIC ACID ANTIBODY

REF Catalog No. 290202, 290302 IVD For *in vitro* diagnostic use only

INTENDED USE

The Meridian Bioscience Endo-Staph® teichoic acid antibody test (TAA) is a standardized, semiquantitative screening procedure for antibodies to staphylococcal ribitol teichoic acid. High titers (≥1:4) of precipitating antibody against staphylococcal ribitol teichoic acid are frequently observed in patients with endocarditis and other deep-seated infections caused by *Staphylococcus aureus*. A negative or low (≤1:2) titer is important in suggesting an absence of underlying staphylococcal disease. (2,23)

EXPLANATION

Diagnosis of deep-seated infections caused by *Staphylococcus aureus* (SA) is confirmed by cultivation of the organism from an appropriate clinical specimen. Bacteremia associated with deep-seated staphylococcal infection presents a puzzling picture to both the clinician and laboratorian since the focus of infection may not be readily apparent. Decisions on the course of antibiotic and surgical therapy depend on both the source and severity of infection. Cultural data alone may be insufficient to demonstrate infection or sepsis due to masking by prior antibiotic therapy. (1,6,10,12,13)

Many authors have described the significance of the teichoic acid antibody test in the diagnosis and management of deep-seated staphylococcal infections. In hospitalized patient populations, positive correlations have been found between high gel diffusion titers (≥1:4) against *Staphylococcus aureus* teichoic acid and the following diseases caused by SA: endocarditis, acute osteomyelitis, deep wound infections, septic arthritis and pneumonitis. In addition, a negative or low titer (<1:4) test has a high correlation with absence of underlying disease of staphylococcal etiology. Finally, the test is described by many authors as useful in the monitoring of therapy, since a falling or rising titer is of significance. (2,4,7,10,20,21,22)

While precipitins for staphylococcal teichoic acid are found in all adult serums, they are present only at low levels (titer <1:4) in uninfected patients which are usually not demonstrable with agar gel diffusion using the purified Endo-Staph® antigen. (7,8,22,23)

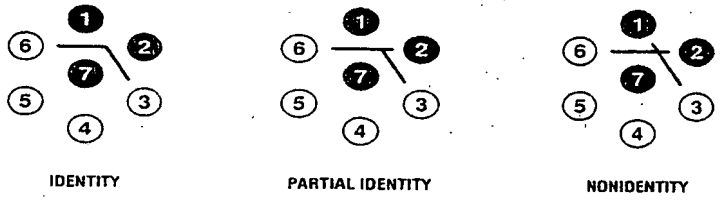
BIOLOGICAL PRINCIPLES

The Meridian Bioscience Endo-Staph® teichoic acid antibody kit is an Ouchterlony double diffusion procedure. High specificity is achieved since the reaction between the patient serum and the antigen is compared to a reference reaction between the control serum and the antigen. (Figure 1)

An antibody and its homologous soluble antigen are placed in separate wells cut in agarose diffusion medium and allowed to diffuse outward. Between the two wells, a concentration gradient of each of the reaction components is established ranging from antigen excess closest to the antibody well, to antibody excess closest to the antigen well. A visible line of precipitate forms at the point of equivalence. (11,12,13)

Antigens or antibodies may be tested for "identity" by placing a test well of the substance in question adjacent to the wells of a known system. If the antigen-antibody complexes are identical, the precipitin lines form an unbroken line of identity with the known system. Partial and nonidentity reactions are also possible. (See Figure 1) A partial identity reaction occurs when certain components of the antigens (or antibodies) are identical and others are not. The "spur" represents the components which are unrelated. A nonidentity reaction will occur when the antigen-antibody complexes are different. The resulting "X" or crossed reaction indicates that two unrelated complexes are present.

Figure 1. Identification of Immunodiffusion Bands



Positive Control, well 1. Patient Serum, well 2. Antigen, well 7

The visualization of the identity reaction—and the use of a highly purified antigen extract of staphylococcal ribitol teichoic acid—eliminate interpretational problems due to cross-reactions with other gram-positive organisms whose cell walls contain other varieties of teichoic acid (e.g., *Streptococcus sp.*, diphtheroids, etc.). (1,4,10,14,23)

COMPONENTS

Reagents available separately:

CATALOG #	PRODUCT	SIZE
290202	Staphylococcal ribitol teichoic acid (purified extract)	2.0 ml
290302	Anti-staphylococcal ribitol teichoic acid	2.0 ml

CAUTION: CONTAINS HUMAN SERUM. HANDLE AS IF CAPABLE OF TRANSMITTING AN INFECTIOUS AGENT.

Each donor unit used in the preparation of this product was tested by FDA approved methods for the presence of antibody to human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2). hepatitis C virus (HCV) and hepatitis B surface antigen (HBsAg) and found to be negative (not repeatedly reactive).

MATERIALS REQUIRED BUT NOT SUPPLIED

Single Series Immunodiffusion Plates (Meridian Catalog #101012)
1.0 ml pipets or tuberculin syringes
Capillary pipets
Reagent grade water
Moist chamber
Indirect light source (optional)

STABILITY AND STORAGE

Shelf life of the Meridian Endo-Staph® TAA reagents is 36 months from the date of manufacture when stored at 4°C. On rehydration, the positive control serum may be stored at refrigerator temperature for up to 1 month, or aliquotted and frozen at -20° for up to one year. After opening the sealed package, the immunodiffusion plates should be stored at 4°C in a humid container.

USER QUALITY CONTROL

The provided positive control serum must be run with each titration to check for an identity reaction. Use of the reagents must be discontinued if the positive control fails to give a precipitin line with the antigen. In addition, a visual examination of the plate should be made to verify that it is adequately hydrated.

PRECAUTIONS

When handling blood specimens, adequate measures should be taken to prevent the dissemination of etiologic agents potentially present in the specimen.

RISK AND SAFETY PHRASES

CONTROL SERA: TOXIC – SODIUM AZIDE

RISK PHRASES:

22 Harmful if swallowed.
32 Contact with acids liberates very toxic gas.

SPECIMEN COLLECTION

For optimal results, sterile serum is obtained from the patient's blood. If a delay is encountered in specimen processing, refrigeration for up to 72 hours is permissible. Specimens may be stored up to six months at -20°C, with no loss of activity, provided they are not repeatedly thawed and refrozen. Specimens in transit between laboratories should be maintained at 4°C for optimal results. Specimens may be preserved with 1:10000 thimerosal or 0.1% sodium azide if necessary.

PERFORMING THE TEST

This test should be performed by qualified personnel per local regulatory requirements.

A. Reagent preparation

Reconstitute the supplied positive control serum by adding 1.0 ml of reagent grade water with a 1.0 ml pipes or tuberculin syringe.

B. Patient serum preparation

Using any convenient amount of patient serum (depending on available pipetor sizes), prepare the following saline dilutions of the serum to be tested: Undiluted, 1:2, 1:4, 1:8, and 1:16. (Note: approximately 40 microliters of each dilution are required for each immunodiffusion well.)

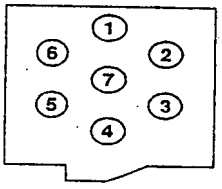
Example:

1) Label five 13 x 75mm serum tubes as follows: #1-Undiluted, #2-1:2, #3-1:4, #4-1:8, #5-1:16.
2) Using a 200 microliter precision pipetor, add 200 microliters of sterile saline to tubes 2 - 5.
3) Using a fresh pipet tip, add 400 microliters of the serum to be tested to tube 1.
4) Transfer 200 microliters from tube 1 to tube 2 and mix thoroughly. Continue transferring and mixing until all required dilutions have been made.
5) Alternatively, dilutions may be prepared using microtiter equipment.

C. Setting up the plate

1) Record the specimen identification number on a fresh immunodiffusion plate and on the provided recording form.
2) Referring to figure 2, or the illustration on the recording form, place an amount of antigen just sufficient to fill the well, without overflowing, in well #7 (center well).

Figure 2.



Control serum well 1, antigen well 7, serum dilutions wells 2-6.

3) Fill well #1 using the provided positive control serum (Anti-staphylococcal ribitol teichoic acid).
4) In clockwise order, place the appropriate patient serum dilution in each well.
5) Carefully close the plate cover, and maintaining the plate in an upright position, place it in a moist chamber at room temperature until diffusion is complete.
6) Evaporation may be further retarded by inverting the plate on completion of diffusion.

D. Reading the test

1) After 24 hours remove the plate from the moist chamber.
2) Using an indirect light source, examine the plate for precipitin lines appearing between the antigen and serum wells.
3) Record precipitin lines on the recording form by drawing the lines in the same position as they appear on the plate.

E. Reporting of results (see also: INTERPRETATION OF THE TEST)

1) The "Teichoic acid antibody titer" is reported as the highest dilution of patient serum at which a precipitin line of identity with the positive control serum is observed.

   Examples:

   a. Teichoic acid antibody titer <1:2 – Within normal range.
   b. Teichoic acid antibody titer = 1:2 – possibility of deep-seated *Staphylococcus aureus* infection: particularly if rising from previous test. Follow-up testing is suggested.
   c. Teichoic acid antibody titer = ≥1:4 – Suggestive of deep-seated *Staphylococcus aureus* infection.

EXPECTED VALUES

Formation of a band of identity with the provided positive control indicates the presence of antibodies to staphylococcal ribitol teichoic acid. In normal, uninfected individuals this identity line may be expected to extend no further than the undiluted serum well. A titer of 1:2 or higher is expected in individuals harboring deep-seated staphylococcal infections. (1,2,3,22)

INTERPRETATION OF THE TEST

Interpretation of the test must be made considering all relevant clinical data pertaining to the patient in question including, but not limited to, cultural data and apparent patient physical status. It is strongly suggested that an infectious disease specialist be consulted before initiation or discontinuance of therapy.

In general, a titer of 1:4 against staphylococcal ribitol teichoic acid is suggestive of a deep-seated staphylococcal infection. The index of suspicion rises in proportion to the titer observed. Formation of a precipitin band with teichoic acid by undiluted patient serum is observed in uninfected individuals, however, uninfected individuals rarely have titers of 1:2 or higher. Many authors suggest longer term anti-staphylococcal therapy for those patients presenting titers of 1:4 or higher. (1,2,3,8,15,16,17,23)

Various authors have reported sensitivity levels of the test for endocarditis ranging from 61-90%. Comparison of results obtained from one study to the next is difficult due to procedural differences such as antigen choice and preparation, agar quality, concentration and pH, and choice of end point. There is a general consensus that patients with skeletal infections (osteomyelitis, in particular) elicit weak (i.e. undilute or 1:2) or occasionally no response to the teichoic acid antigen. (8,9,10,14,20,21)

High specificity is inherent in the Ouchterlony double diffusion procedure, since precipitin lines due to cross reacting factors may be visualized as "nonidentity" reactions. (14))

LIMITATIONS OF THE TEST

Patients with skeletal infections may elicit weak, or no antibody response to staphylococcal ribitol teichoic acid.

Occasional weak titers (Undiluted, 1:2) may be expected in uninfected individuals.

A negative teichoic acid antibody test result does not exclude the diagnosis of deep-seated staphylococcal infection.

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23. Unpublished data on file. Meridian Bioscience. Inc.

CE

INTERNATIONAL SYMBOL USAGE

You may see one or more of these symbols on the labeling/packaging of this product

	Manufactured by		For Performance Evaluation Only
AR	Authorized Representative		Temperature Limitations
REF	Catalog Number		Use By/Expiration Dating Information
IVD	*In vitro* Diagnostics	Σ	Sufficient for "X" Tests
LOT	Batch Code/Lot Information	CE	CE Symbol

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